NCI Cooperative Group Data Monitoring Committee Policy

Studies to be Monitored:

One or more Data Monitoring Committees (DMC) will be established to monitor all phase III therapeutic clinical trials of the cooperative group. Whereas a single DMC per group is acceptable and may provide the most feasible way of maximizing independence of the DMC, separate DMC's could be considered for single large trials, especially those that involve substantial risk/benefit oversight.

Responsibilities:

1. The primary responsibility of the DMC is to review interim analyses of outcome data (prepared by the study statistician) and to recommend whether the study needs to be changed or terminated based on these analyses. The committee also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.

2. The DMC reviews reports of related studies performed by the Groups or other organizations to determine, considering information and recommendations supplied by the study committee, whether the group study needs to be changed or terminated.

3. The DMC reviews interim toxicity data although that is primarily the responsibility of the study committee.

4. The DMC reviews major modifications to the study proposed by the study committee prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size).

Membership:

DMC members will be appointed for a fixed term by the Group Chair or his/her designee with the approval of the CTEP Associate Director or his/her designee. The nominees should be reviewed and approved by CTEP prior to their appointment. The committee will include physicians and statisticians from within and outside the Group selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of same), and knowledge of good clinical trial methodology. The committee should include a consumer representative and a voting statistician from outside the group. A CTEP physician and a CTEP statistician will be non-voting members and must be free to attend all sessions of the DMC, including closed and executive sessions. The Group Statistician will not be a voting member of the DMC. A majority of the voting DMC members will not be affiliated with the Cooperative Group. Group members who are members of the DMC should see themselves as primarily representing patient interests, and not Group or Group-chair interests. Members of a

study committee or leadership of the disease committee (e.g., chair or vice-chair of the disease committee) conducting a study will excuse themselves from all DMC discussions concerning that study and will not receive DMC reports concerning that study. Additionally, the study statistician will not be a voting member of the DMC for his/her trial. The size of the DMC should be limited, and it is unlikely that more than 10 people would be required to constitute a DMC.

The Group Chair will not attend meetings of the DMC, with the exception of a DMC that has no voting members belonging to that Cooperative Group. In this case, the Group Chair or his/her designee may attend the meetings as a non-participating observer.

Meetings:

DMC meetings will be held at least once every six months. Each randomized clinical trial should have specified interim analysis times, although the DMC should be apprised at each meeting of the status of all trials for which it is responsible, e.g., accrual, toxicity concerns, and the next formal monitoring date as specified in the protocol.

It is recommended that a written report outlining the current status of each trial to be monitored be sent to the DMC members by the study statistician at least three weeks prior to the DMC meeting. The Study Chair may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study. The statistician's report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up and whether DMC discussion is needed. In the event a study will be considered for closure due to slow accrual, the CTEP members of the DMC may discuss with other CTEP staff the possibility of early closure due to slow accrual. Although no confidential information would be disclosed, this would allow the CTEP members of the DMC to bring to the DMC meeting any information from CTEP concerning early closure that might be useful in the DMC deliberations.

The review of each trial may include three parts. The first part will be an open session in which members of the study team and disease committee may be present at the request of the DMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues, and no outcome results may be presented. Following the open session, there will be a closed session limited to DMC members and possibly the study statistician in which outcome results will be presented either by a member of the DMC, the Group Statistician, or the study statistician. Following this closed session, there will be a fully closed, executive session in which the DMC discusses outcome results, and then votes. At the executive session, those present are limited to DMC members.

Recommendations:

DMC recommendations should be based upon results for the current study being monitored as well as upon data available to the DMC from other related studies. The study committees and DMC members will assure that the DMC is advised about relevant non-confidential results from other related studies that become available. It will be the responsibility of the DMC, with advice

from the study committee, to determine the extent to which this information is relevant to decisions to continue or modify the current study.

The DMC will provide recommendations to the Group Chair to change a study or to continue a study unchanged. The study statistician may send his/her written report prepared prior to the DMC meeting to the Group Chair at this time. In the event a change is recommended by the DMC, the Group Chair may seek the advice, in a confidential manner, of the Study Chair, Disease Committee Chair, and/or Group Statistician.

a. In the event that the DMC recommends a study change for patient safety reasons (including early stopping of inferior therapy), the Group Chair will act to implement the change as expeditiously as possible. In the unlikely situation that the Group Chair does not concur with the DMC recommendation, then the CTEP Associate Director must be informed of the recommendation of the DMC and of the Chair's reasons for disagreeing with the recommendation. The CTEP Associate Director and the Group Chair, in consultation with the DMC Chair, will be responsible for reaching a mutually acceptable decision about the study. Confidentiality will be maintained during these discussions, but relevant data will be shared with the Group Chair, CTEP Associate Director, and other parties whom they wish to involve in reaching a decision.

b. In the event that the DMC recommends a study be closed early due to slow accrual, provided that the CTEP members of the DMC have been previously informed of this possibility, then the recommendation of the DMC would be processed as in (a).

c. In the event that the DMC recommends a change in a study for reasons other than either patient safety (e.g., to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DMC will provide to the Group Chair an adequate rationale. In the absence of disagreement, the Chair will be responsible for having an amendment prepared and submitted to CTEP reflecting the recommendations of the DMC and providing the rationale for the changes. CTEP approval of the amendment will be required prior to implementation of the change, although it is anticipated that a decision to override the DMC's recommendation will be made only in the most exceptional circumstances.

Confidentiality Procedures:

No communication of the deliberations or recommendations of the committee, either written or oral, should be made outside of the committee except as provided for in these policies and procedures. Statements of confidentiality should be signed by all DMC members. Outcome (efficacy) results are strictly confidential and must not be divulged to *any* non-member of the DMC (excepting the Group Chair and CTEP Associate Director as described above) without the approval of the DMC until the recommendation to report the results are accepted and implemented.

Release of Results:

Any planned release of outcome data [either internal to the group, to NCI personnel not members of the committee, or external (e.g., paper presented at professional society meetings, seminars, papers, etc.)] prior to the final approval of general dissemination of results must be reviewed and approved by the DMC. In general, outcome data would not be routinely made available to individuals outside of the DMC until accrual has ceased and all patients have concluded their randomized treatment. After this timepoint, the DMC may approve the release of outcome data on a confidential basis to the Study Chair for planning the preparation of manuscripts, and/or to a small group of individuals for purposes of planning future trials. The DMC will consider special requests for information from the disease committee chair prior to that timepoint. The DMC should be made aware of any communication of analysis results outside of the statistical center at any time.

Conflict of Interest:

Individuals invited to serve on the DMC (voting and non-voting) will disclose to the Group Chair any potential, real or perceived conflicts of interest. These will include professional interest, proprietary interest and miscellaneous interest considerations as described in the attached conflict of interest policy. The Group Chair, with the advice of an ad-hoc committee, will review possible conflicts and determine whether there is sufficient basis to exclude the individual from serving on the DMC. Potential conflicts which develop during the conduct of a trial should also be disclosed to the Group Chair.

Intergroup Trials:

These guidelines apply also to intergroup trials. The DMC of the Group whose statistical center is coordinating the trial will monitor the trial. The term "Group Chair" in this document will apply to the Chair of the coordinating Group.

CTEP Oversight:

In order to satisfy its objectives of protecting patients, ensure study integrity and assure public confidence in the conduct of clinical trials, it is essential that the DMC function in a manner that demonstrates competence, experience and independence of Group, career or financial interests. If CTEP determines that a DMC for a group is not functioning in this manner, it will discuss with the Group Chair what changes are needed to the composition or structure of the DMC.

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